REMARKS

I. Claims

Claims 1-24, 26, and 51-54 are pending in the instant application. Claims 1 and 24 have been amended. Claims 25 and 27-50 have been canceled. Claims 51-54 have been added.

Claim 1 has been amended to recite that the microparticles have a "a mean dimension of less than 1mm" and that the preparation is parenterally administered "wherein said first polymeric coating maintains structure integrity during said sustained release period." Support for this amendment can be found at ¶¶ [0030] and [0042].

Claim 24 has been amended to incorporate the limitation from now-canceled claim 25, *i.e.*, so that the pharmaceutical preparation is in "the form of a suspension of said coated microparticles in a pharmaceutically acceptable carrier."

Claim 51 is directed to a pharmaceutical preparation for sustained-release of an active pharmaceutical ingredient after parenteral administration. Claim 51 is similar to claim 1, however, the last wherein clause recites "wherein the first polymeric coating is water permeable." Support for this claim can be found throughout the specification. Support for this wherein clause can be found at ¶¶ [0037]-[0038] and [0053].

Claim 52 is directed to a pharmaceutical preparation for sustained-release of an active pharmaceutical ingredient after parenteral administration. Claim 52 is similar to claim 1, however, the last wherein clause recites "wherein the weight of the first polymeric coating is between 0.1% and 200% of the weight of the core particle." Support for this claim can be found throughout the specification. Support for this wherein clause can be found at ¶¶ [0023] and [0064].

Claim 53 is directed to a pharmaceutical preparation for sustained-release of an active pharmaceutical ingredient after parenteral administration. Claim 53 is similar to claim 1,

however, the last wherein clause recites "wherein the weight of the first polymeric coating is between 0.1% and 200% of the volume of the core particle." Support for this claim can be found throughout the specification. Support for this wherein clause can be found at ¶¶ [0024] and [0064].

Claim 54 is directed to a pharmaceutical preparation for sustained-release of an active pharmaceutical ingredient after parenteral administration. Claim 53 is similar to claim 1, however, the last wherein clause recites "wherein the sustained release period is at least five days." Support for this claim can be found throughout the specification. Support for this wherein clause can be found at ¶ [0109] and FIG. 1.

No new matter has been added by these amendments.

II. Interview Summary

Applicant thanks Examiner Young and Supervisory Examiner Jones for the personal interview conducted on August 13, 2010 at the United States Patent and Trademark Office. Applicant appreciates and thanks Examiner Young and Supervisory Examiner Jones for taking the time to meet and for providing suggested amendments for the claims. Applicant has attempted to incorporate those suggestions into claim 1 and into the four new independent claims (claims 51-54).

III. Claim rejections under 35 U.S.C. § 102

A. U.S. Patent No. 5,271,946 to Hettche et al.

Claims 1-5, 9-20, 24-30, 34-42, and 45-46 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hettche et al., U.S. Patent No. 5,271,946 (hereinafter "the '946 patent"). (Office Action, p. 2). The Office Action states that Applicant's arguments filed March 25, 2010 were fully considered but not found to be persuasive. (Office Action , p. 9). Applicant respectfully traverses this rejection and fully incorporates by reference all of Applicant's previous remarks regarding the '946 patent into this Response.

The Office Action states that "Example 5 clearly discloses multiple coated drug cores." (Office Action, p. 9). Applicant respectfully disagrees. Example 5 reads, in pertinent part:

> 100 g of azelastine hydrochloride, 200 g of tartaric acid, 500 g of lactose and 700 g of microcrystalline cellulose are mixed and made up into a paste with about 700 g of purified water. The moist mass is pressed through a perforated plate of hole diameter 1 mm and the resulting strands are divided and rounded in a conventional manner on a spheronizer disc. The pellets obtained are dried and sieved.
>
> 1000 g of the pellets of sieve fraction 800 to 1250 μm are sprayed with a suspension …
>
> (col. 14, lines 13-21).

This is quite different from the presently claimed preparations, which comprise core particles comprising active pharmaceutical ingredient and a polymeric coating *on those core particles*. There are no coated core particles in Example 5 of the '946 patent. Example 5 simply discloses a mixture of azelastine hydrochloride, tartaric acid, lactose, and microcrystalline cellulose that is pressed into pellets that are then coated. Size 3 hard gelatin capsules are then filled with the coated pellets. The gelatin capsules cannot be the presently claimed microparticles comprising coated core pellets because the presently claimed microparticles have a mean dimension of less than 1mm. Size 3 hard gelatin capsules are significantly larger. Moreover, the '946 patent does not teach that the size 3 hard gelatin capsules are capable of being administered parenterally, as the instantly claimed preparations are.

Additionally, Example 5 does not teach that microcrystalline cellulose is coated onto particles. Rather, it is simply mixed with the azelastine hydrochloride, tartaric acid, and lactose. This teaches away from the instant claims which recite that the polymeric coating be *on* the core particles. The specification of the instant application explains why such mixing of the polymer was a problem in the prior art. The specification reads, in relevant part:

> [0057] When preparing the coated microparticles of the invention, a core particle comprising the active pharmaceutical ingredient is coated with a first polymer-forming solution which forms the first

> polymeric coating. ... To avoid the problems of the prior art, however, it is desirable to reduce or minimize the dissolution of the active pharmaceutical ingredient in the first polymer-forming solution ***and the consequent formation of a polymeric coating with the active pharmaceutical ingredient interspersed with the polymeric material***.
>
> (***emphasis added***).

Example 5 goes on to describe how the pellets are spray-coated with a suspension. Again, this is very different than the instantly claimed pharmaceutical preparations. In the instant claims, the microparticles comprise *coated* core particles. The coated pellets of Example 5 do not comprise coated particles.

> Example 5 also does not teach that the substances used to coat the pellets must be permeable to the active ingredient. Such permeability is a limitation of the instantly claimed preparations that is not found in the '946 patent. Without such a teaching in the '946 patent, a person of ordinary skill in the art would not understand which polymers to use with which active pharmaceutical ingredients to arrive at the sustained release pharmaceutical preparations of the instant claims.

The '946 patent also does not teach that the active pharmaceutical ingredient forms a saturated solution within the microparticles after being administered parenterally, as presently claimed. The ability of the active pharmaceutical ingredient to form a saturated solution within the coated microparticles is yet another element of the presently claimed pharmaceutical preparations that is not found in the '946 patent.

The Office Action also cites Example 3 for disclosing coated drug particles. (Office Action, p. 9). However, Example 3 does not teach the claimed preparations for reasons similar to Example 5. Example 3 reads, in pertinent part:

> 50 g of azelastine HCl are mixed with 100 g of tartaric acid, 250 g of lactose, 10 g of microcrystalline cellulose (Avicel PH 101) and 7 g of hydroxypropyl cellulose [viscosity of the 5% solution: 75 to 150 cps (e.g. trade name: Klucel LF)] and the mixture made up into a paste with 60 g of a 6.25% aqueous solution of

> hydroxypropyl cellulose (viscosity of the 5% aqueous solution: 75 to 150 cps (e.g. trade name Klucel LF)). The moist mass is pressed through a perforated plate having a hole diameter of 1mm and the resulting strands are divided and rounded in the conventional manner by treatment on a spheronizer disc. The pellets obtained are dried and sieved. 300 g of pellets of the sieve fraction 800 to 1200 µm are coated in the conventional manner with a solution of 42.5 g of ethyl cellulose (trade name: Ethocel 30 Type N 22), and 37.5 g of polyethylene glycol 1500 (trade name e.g. Carbowax 1540) in 720 g of chloroform through spraying in a fluidized bed apparatus.
>
> 50 mg of the above obtained coated pellets are filled into size 3 hard gelatin capsules.
>
> (col. 13, lines 15-35).

As in Example 5, the coating does not occur in Example 3 until after the azelastine HCl tartaric acid, lactose, microcrystalline cellulose, and hydroxypropyl cellulose are mixed together, made into a paste, and then formed into pellets. The coating is applied *to the pellets*. Again, this is very different from the presently claimed preparations, where the microparticles comprise *coated* core particles.

Moreover, as in Example 5, Example 3 teaches that the coated pellets are filled into size 3 hard gelatin capsules. The Office Action states that "[t]his constitutes a multiparticulate dosage form comprising coated drug cores." (Office Action, p. 9). As discussed above, the gelatin capsules are very different from the presently claimed microparticles comprising coated core pellets because the presently claimed microparticles have a mean dimension of less than 1mm. Size 3 hard gelatin capsules are significantly larger. Furthermore, the '946 patent does not teach that the size 3 hard gelatin capsules are capable of being administered parenterally, as the instantly claimed preparations are.

The Office Action also asserts that the release kinetics of the claimed preparations are disclosed by the '946 patent because those kinetics are inherent in the compositions disclosed in the '946 patent. (Office Action, p. 3). However, as can be seen by the data in column 16 of Example 9 of the '946 patent, the release of the azelastine was highly non-linear. Such a release

profile is very different from the pseudo-zero-order release profile that can be obtained with the claimed preparations of the instant application. The non-linear profile of the compositions of the '946 patent flatly contradicts the assertion in the Office Action that the claimed sustained release profile is inherent in the '946 patent's compositions. Moreover, this non-linear profile further illustrates the difference between the compositions disclosed in the '946 patent and the claimed preparations. The '946 patent provides no teaching of how to obtain a sustained release profile with the claimed preparations.

Finally, the '946 patent does not teach that the first polymeric coating maintains structural integrity during said sustained-release period or that the sustained-release period is at least five days, as now recited in claims 1 and 54, respectively.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989); Patent and Trademark Office, MANUAL OF PATENT EXAMINING PROCEDURE § 2131 (8th ed. July 2008 Revision). Because the '946 patent does not teach each and every element of the claimed preparations, the '946 patent does not anticipate the amended claims.

Based on the foregoing, Applicant respectfully requests that the rejection of claims 1-5, 9-20, 24-30, 34-42, and 45-46 under 35 U.S.C. § 102(b) based on the '946 patent be withdrawn.

B. **U.S. Patent No. 5,133,974 to Paradissis et al.**

Claims 1-4, 6, 9-19, 24-25, 27-31, 34-42, and 44-45 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Paradissis et al., U.S. Patent No. 5,133,974 (hereinafter "the '974 patent"). (Office Action, p. 3). The Office Action states that the "it remains the position of the Examiner of the '974 patent continues to anticipate the instant claims." (Office Action, p. 10). Applicant respectfully traverses this rejection and fully

incorporates by reference all of Applicant's previous remarks pertaining to the '974 patent into this Amendment and Response.

The Office Action states that "Applicant argues that the '974 patent does not disclose a sustained release preparation however extended release particles are formed by coating the immediate release particles with polymers (col. 8, lin. 1-5)." (Office Action, p. 10). This is very different from the claimed preparations. The cited portion of the '974 patent reads:

> The extended release pharmaceutical formulation of the present invention may be comprised of two main components: the immediate release particles and extended release particles. The immediate release particles and extended release particles may be blended together and filled into hard gelatin capsules or formed into tablets with standard equipment.
>
> A particularly preferred extended release pharmaceutical formulation according to the invention is comprised of a mixture of: ...
>
> (col. 7, line 65 – col. 8, line 6).

This pharmaceutical formulation is quite different from the claimed pharmaceutical preparations. As acknowledged by the Examiner, "the core particles comprising a drug are coated to a sugar sphere." (Office Action dated 9/25/2009, p. 4). This is the "immediate release particle." ('974 patent, col. 4, lines 12-20). "The immediate release particle core additionally contains an inert spherical substrate particle which aids in the diffusion/release of the drug from the formulation." (col. 5, lines 23-26). "The drug adheres to the inert spherical substrate particle through a binding agent which is preferably applied by a suitable solvent. (col. 5, lines 38-40).

To obtain the extended release particles, the immediate release particles are coated with a plasticizer and a film forming material as part of its dissolution modifying system. (col. 6, line 19 – col. 7, line 10). Thus, the extended release particles of the '974 patent comprise active pharmaceutical ingredient with a binder to adhere the active pharmaceutical ingredient to an inert spherical carrier that is then coated with a plasticizer and a film forming material. This is starkly different from the presently claimed sustained-release preparations, which comprise core

particles comprising an active pharmaceutical ingredient and a polymeric coating on those core particles, without the addition of a second film forming agent or a plasticizer. The coated extended release particles do not comprise coated particles. Furthermore, there is no teaching that the gelatin capsules comprising uncoated immediate release particles and coated immediate release particles have a mean dimension of less than 1 mm. This is very different from the presently claimed preparations which comprise *coated* microparticles that have a mean dimension of less than 1 mm and that comprise *coated* core particles that comprise the active pharmaceutical ingredient.

The '974 patent also does not disclose that the active pharmaceutical ingredient "forms a saturated solution within said coated microparticles after said administration," as presently claimed. The ability of the active pharmaceutical ingredient to form this saturated solution is a limitation of the claimed sustained-release preparations. Furthermore, the '974 patent does not disclose that the binder is "permeable to said active pharmaceutical ingredient," as presently claimed with respect to the first polymeric coating. Thus, the '974 patent fails to teach these two elements of the instant claims.

The '974 patent also discloses that its formulations are matrices. For example, the '974 patent states:

> In particular it is essential to use starting components of drug and inert carriers which have mesh sizes greater than 200 mesh. Such sizes aid in offering various advantages. First, they assist in making hard granules which improves the binding characteristics of the matrix.
>
> (col. 7, lines 30-35).

The '974 patent also states:

> By employing the formulations of the invention, one is able to achieve an extended release system which is a dynamic system composed of wetting, hydrating and dissolution components. At the same time, other soluble materials or drugs will also wet, dissolve and diffuse out of the matrix while insoluble materials

> will be held in place until the surrounding encapsulation layer erodes or dissolves away.
>
> (col. 7, lines 42-49).

The pharmaceutical preparation of the claims of the instant application are not a matrix, but comprise core particles comprising active pharmaceutical ingredient and a polymeric coating on those core particles. The difference between the claimed preparations and a matrix is described, for example, in the specification at ¶ [0054], which states, in pertinent part:

> [0054] If the active pharmaceutical ingredient and the first polymer-forming solution are both hydrophobic or hydrophilic, the core particle may partially or completely dissolve in the polymer-forming solution, resulting in microparticles in which the active pharmaceutical ingredient is interspersed or embedded in a matrix of the polymer as opposed to being coated by the polymer.

The specification describes the advantages of the present invention over the matrices formed in the prior art at ¶¶ [0059] and [0063], which read as follows:

> [0059] Moreover, many active pharmaceutical ingredients and many commonly-used polymer-forming solutions are hydrophobic in nature. As a result, core particles of such active pharmaceutical ingredients tend to dissolve in many commonly-used polymer-forming solutions if the solutions are applied directly, resulting in microparticles in which the active pharmaceutical ingredient is interspersed or embedded in a matrix of the polymer as opposed to being coated by the polymer. Depending upon the degree of dissolution, such microparticles may not exhibit pseudo-zero-order kinetics of release. Therefore, a first polymeric coating can be employed which is formed from a hydrophilic first polymer-forming solution in which the active pharmaceutical ingredient is substantially insoluble. A second polymeric coating formed from a hydrophobic second polymer-forming solution can then be employed without dissolving the active pharmaceutical ingredient. Conversely, for hydrophilic active pharmaceutical ingredients, a first polymeric coating can be formed from a hydrophobic first polymer-forming solution followed by a second polymeric coating formed from a hydrophilic second polymer-forming solution.
>
> ...

> [0063] In addition, in contrast to prior art sustained-release particle formulations, the core particles of the present invention constitute a substantially larger portion of the overall volume and weight of the coated microparticles and, conversely, the polymeric coating(s) constitute a substantially smaller portion. This is advantageous because the overall volume of microparticles which must be administered per unit weight of the active pharmaceutical ingredient is reduced relative to the prior art particles in which the active pharmaceutical ingredient is dissolved or interspersed in a relatively large volume and weight of polymeric matrix material which releases the active pharmaceutical ingredient as it degrades. This advantage arises from the different mechanism of action of the coated microparticles of the invention, in which a relatively thin polymeric coating can contain a relatively large core which contains a saturated solution of the active pharmaceutical ingredient and permits release by diffusion with pseudo-zero-order kinetics.

Thus, the pharmaceutical preparations of the claims of the instant application are not matrices.

In addition to requiring plasticizers and film forming materials, the '974 patent is also directed solely to pharmaceutical formulations for oral administration. When describing which drugs may be used in its formulations, the '974 patent states that a "wide variety of medicaments which are orally administered both in tablet, capsule and particulate form may be used to prepare particles according to this invention." (col. 4, lines 26-29; emphasis added). The '974 patent also states that the "formulations of the invention are administered orally to mammals in suitable amounts to achieve the drug efficacy sought." (col. 9, lines 25-27). The '974 patent provides no teaching and makes no mention of parenteral administration. The Office Action contends that "the claims actually recite that the particles are capable of parenteral administration, meaning there must only be a possibility of the particles being administered in this way given a certain set of circumstances. This is a future intended use that does not change the compositional components of the instant invention and do not distinguish over the future art." (Office Action, p. 11). The claims have been amended to recite "parenteral administration of said preparation suspended in a pharmaceutically acceptable carrier." The '974 patent does not teach or suggest

that the gelatin capsules are capable of being parenterally administered when suspended in a pharmaceutically acceptable carrier. As such, the '974 patent does not teach this claim limitation.

Finally, the '974 patent does not teach that the polymeric coating maintains its structural integrity during the sustained-release period. In fact, the '974 patent teaches away from this because the encapsulation layer degrades during the sustained-release period. The '974 patent states:

> By employing the formulations of the invention, one is able to achieve an extended release system which is a dynamic system composed of wetting, hydrating and dissolution components. At the same time, other soluble materials or drugs will also wet, dissolve and diffuse out of the matrix while insoluble materials will be held in place ***until the surrounding encapsulation layer erodes or dissolves away***.
>
> (col. 7, lines 42-49) (***emphasis added***).

Additionally, the '974 patent does not teach a sustained-release period of at least five days, as recited in claim 54. In fact, the '974 patent states that its "system is formulated to each drug profile to permit a release of the drug from the particles over a 12 to at least 24 hour period." (col. 6, lines 31-33). Such a system cannot achieve the pseudo-zero-order release profile of the instantly claimed preparations for a sustained-release period of at least five days.

As noted above "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989); Patent and Trademark Office, MANUAL OF PATENT EXAMINING PROCEDURE § 2131 (8th ed. July 2008 Revision). As discussed, the '974 patent does not teach or suggest each and every element of the instant claims.

Based on the foregoing, Applicant respectfully requests that the rejection of claims 1-4, 6, 9-19, 24-25, 27-31, 34-42, and 44-45 under 35 U.S.C. § 102(b) based on the '974 patent be withdrawn.

C. **U.S. Patent No. 5,286,497 to Hendrickson et al.**

Claims 1-4, 6, 9-12, 16-19, 24, 27, and 43 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hendrickson et al., U.S. Patent No. 5,286,497 (hereinafter "the '497 patent"). (Office Action, p. 5). The Office Action states that "it remains the position of the Examiner that the '497 patent continues to anticipate the instant claims." (Office Action, p. 11). Applicant respectfully traverses and fully incorporates by reference all of Applicant's previous remarks pertaining to the '497 patent into this Amendment and Response.

The Office Action states that the '497 patent teaches:

> a sustained release formulation comprising multiple coated beads that exhibit zero-order release of an active agent (abstract, Figures). The beads comprise a core bead that is formed from compression (col. 6, lin. 10-16). The core comprises the drug and comprises a binding solution coated to the drug in order to keep the drug in place (col. 5, lin. 20-25). The binder solution comprises cellulose, vinyl and acrylic based polymers (col. 5, lin. 25-35). The coated drug core is further coated with a second polymeric coating comprising an acrylic based polymer (col. 6, lin. 10-50). The coated beads have a size range from 354-595 microns (col. 4, lin. 50-55).
>
> (Office Action, p. 5).

The '497 patent discloses that a "new diltiazem formulation has been discovered that will optimize blood levels of diltiazem over a 24 hour period by decreasing the variance between peak and trough levels of diltiazem. The formulation is a controlled release dosage form which exhibits an *in vitro* stair stepped release profile." (col. 2, lines 60-66). This stair-stepped release profile is also illustrated in the data shown in FIG. 1-3. Such a stair-stepped release profile is quite different from the pseudo-zero-order kinetics of the preparations of the instant claims. This is because the '497 patent discloses delayed release of diltiazem, not sustained-release. It is the

sustained-release aspect of the instantly claimed pharmaceutical preparations that provides the pseudo-zero-order kinetics. Moreover, this stair-stepped release profile contradicts the Office Action's assertion that the pseudo-zero-order release kinetics of the instantly claimed preparations are an inherent functional limitation disclosed by the '497 patent. Clearly, such a limitation is neither disclosed nor inherent given the stair-stepped release profiles of the compositions disclosed by the '497 patent. This is because the preparations disclosed in the '497 patent are very different from the claimed preparations. There is no teaching in the '497 patent of how to obtain a pharmaceutical preparation having sustained release profile.

To achieve a "controlled" release dosage form, the '497 patent teaches a blend of rapid release diltiazem beads and delayed release diltiazem beads. (col. 3, lines 16-18). This difference between the '497 patent and the instant claims is further illustrated by the description of the diltiazem beads:

> Both the rapid release diltiazem beads and the delayed release diltiazem beads are comprised of two parts. The first part is a central core which contains the diltiazem or a pharmaceutically acceptable salt thereof in association with conventional excipients (diltiazem blend). The central core of the rapid release diltiazem beads and the delayed release diltiazem beads may be identical and preferably are.
>
> (col. 4, lines 26-33).

Thus, the delayed release beads comprise a central core comprising diltiazem. There is, however, no teaching that the delayed release beads comprise a permeable polymeric coating or that the active pharmaceutical ingredient forms a saturated solution within a microparticle.

Similar to the '974 patent, the '497 patent discloses only diltiazem formulations for oral administration. The '497 patent states:

> The blended diltiazem beads may be administered by a number of dosage forms known in the art. For example, they may be placed into soft or hard gelatin capsules. The blended beads may be admixed with a binder such as microcrystalline cellulose and

> compressed into tablets. Alternatively, they may be placed in a liquid immediately prior to administration and administered as a suspension. Methods for producing these various dosage forms are known to those skilled in the art.

The '497 patent provides no teaching and makes no mention of parenteral administration. This is quite different from the claimed preparations for sustained-release of an active pharmaceutical ingredient after parenteral administration of the preparations suspended in a pharmaceutically acceptable carrier.

As discussed above, the claims of the instant application are directed to a pharmaceutical preparation for sustained-release of an active pharmaceutical ingredient after parenteral administration, wherein the active pharmaceutical ingredient forms a saturated solution within the microparticles after the parenteral administration. There is no teaching in the '497 patent that polymeric coating is permeable to the active pharmaceutical ingredient, as presently claimed. Moreover, the '497 patent does not teach that the active pharmaceutical ingredient forms a saturated solution within the microparticles, as presently claimed.

Furthermore, the '497 patent does not teach a "sustained-release period of at least five days," as recited in claim 54. In fact, the '497 patent is directed to "[a] new diltiazem formulation … that will optimize blood levels of diltiazem over a 24 hour period …" (col. 2, lines 61-64). Such a formulation cannot achieve the pseudo-zero-order release profile of the instantly claimed preparations for a sustained-release period of at least five days.

Finally, the '497 patent does not teach that the polymeric coating maintains its structural integrity during the sustained-release period, as recited in claim 1.

As also discussed above, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989); Patent and Trademark

Office, MANUAL OF PATENT EXAMINING PROCEDURE § 2131 (8th ed. July 2008 Revision). Because the '497 patent does not teach each and every element of the claimed preparations, the '497 patent does not anticipate the amended claims.

Based on the foregoing, Applicant respectfully requests that the rejection of claims 1-4, 6, 9-12, 16-19, 24, 27, and 43 under 35 U.S.C. § 102(b) based on the '497 patent be withdrawn.

IV. Claim Rejections under 35 U.S.C. § 103

A. U.S. Patent No. 5,133,974 to Paradissis et al.

Claims 1, 6-8, and 31-33 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the '974 patent to Paradissis. (Office Action, p. 7). Applicant respectfully traverses this rejection and fully incorporates by reference all of Applicant's previous remarks pertaining to the '974 patent into this Response.

The Office Action states that "the instant claims recite that the claims are merely capable of parenteral administration meaning that the formulation can be used for parenteral administration given a specific set of circumstances. These limitations are a future intended use that do not distinguish over the prior art." (Office Action, p. 12). The claims have been amended to recite "parenteral administration of said preparation suspended in a pharmaceutically acceptable carrier." The '974 patent does not teach or suggest to a person of ordinary skill in the art how to parenterally administer the gelatin capsules suspended in a pharmaceutically acceptable carrier, as instantly claimed. As such, the '974 patent does not teach or suggest this claim limitation.

The Office Action also asserts that "it would have been obvious to choose smaller particles from the wide range of particles produced because these particles would have an increase surface area increasing the total amount of pharmaceuticals administered to the patient." (Office Action, p. 13). This is different from the presently claimed sustained-release preparations, which comprise core particles comprising an active pharmaceutical ingredient and a polymeric coating on those core particles, wherein the active pharmaceutical ingredient forms a

saturated solution within the coated microparticles after the parenteral administration. This limitation illustrates that it is not simply a matter of choosing smaller particles to obtain the sustained release kinetics of the claimed preparations. The '974 patent also does not teach or suggest that the active pharmaceutical ingredient "forms a saturated solution within said coated microparticles after said administration," as presently claimed. The ability of the active pharmaceutical ingredient to form this saturated solution is a limitation of the claimed sustained formulations that allows for sustained release of the active pharmaceutical ingredient. Furthermore, the '974 patent does not disclose that the binder is "permeable to said active pharmaceutical ingredient," as presently claimed with respect to the first polymeric coating. Without teaching that the polymeric coating be permeable, a person of ordinary skill in the art would not understand which polymers to use with which active pharmaceutical ingredients to arrive at the sustained release pharmaceutical preparations of the instant claims. Accordingly, the '974 patent fails to teach these two elements of the instant claims.

Even if the '974 patent discloses particles from 250-2000 microns, as the Office Action contends, there is no teaching or suggestion in the '974 patent to formulate a pharmaceutical preparation for parenteral administration comprising microparticles that have a mean dimension of less than 1 mm and that comprise core particles comprising an active pharmaceutical ingredient and a polymeric coating on those core particles, wherein the preparation is suspended in a pharmaceutically acceptable carrier for parenteral administration, wherein the active pharmaceutical ingredient forms a saturated solution within the coated microparticles, wherein the polymeric coating is permeable to the active pharmaceutical ingredient, and wherein the particle sizes are as claimed in claims 6-8 and 31-33. Accordingly, a person of skill in the art would not have understood or been motivated to modify the '974 patent to develop the claims of the instant application.

Based on the foregoing, Applicant respectfully requests that the rejection of claims 1, 6-8, and 31-33 under 35 U.S.C. § 103(a) based on the '974 patent be withdrawn.

B. **U.S. Patent No. 5,271,946 to Hettche et al.**

Claims 1, 21-23, and 48-50 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the '946 patent to Hettche. (Office Action, p. 7). Applicant respectfully traverses and fully incorporates by reference all of Applicant's previous remarks pertaining to the '946 patent into this Response.

The Office Action asserts that "... Examples 3-5 recite cores that are coated. These cores are coated and collected into a gelatin capsule. This meets the limitations of the instant claims regarding multi-particulate dosage forms." (Office Action, p. 13). As discussed above, the gelatin capsules cannot be the presently claimed microparticles comprising coated core pellets because the presently claimed microparticles have a mean dimension of less than 1mm. Size 3 hard gelatin capsules are significantly larger. Moreover, the '946 patent does not teach that the size 3 hard gelatin capsules are capable of being administered parenterally, as the instantly claimed preparations are. Furthermore, the Examples do not teach that microcrystalline cellulose is coated onto particles. Rather, it is simply mixed with the azelastine hydrochloride, tartaric acid, and lactose. As discussed above, this teaches away from the instant claims which recite that the polymeric coating be *on* the core particles.

The Office Action also asserts that because the same polymers are disclosed, then the permeability of the coating is also disclosed. (Office Action, p. 13). However, Example 5 does not teach that the substances used to coat the pellets must be permeable to the active ingredient. Such permeability is a limitation of the preparations of the instant claims that is not found in the '946 patent. Without such a teaching in the '946 patent, a person of ordinary skill in the art would not understand which polymers to use with which active pharmaceutical ingredients to arrive at the sustained release pharmaceutical preparations of the instant claims.

By mixing, rather than coating, the active pharmaceutical ingredient with a sustained release component, by failing to teach microparticles having a mean dimension of less than 1 mm and comprising coated core particles, by failing to teach a polymeric coating that is permeable to the active pharmaceutical ingredient, by failing to teach that the active

pharmaceutical ingredient forms a saturated solution within the microparticle, by failing to teach that the polymeric coating maintains its structural integrity during the sustained-release period, and by failing to teach a sustained-release period of at least five days, the '946 patent does not teach or suggest the instantly claimed sustained-release preparations.

Based on the foregoing, Applicant respectfully requests that the rejection of claims 1, 21-23 and 48-50 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicant believes the rejections have been overcome and the claims are in condition for allowance. Applicant respectfully requests that a timely Notice of Allowance be issued.

Other than the fee for a three-month extension of time and the fees for the Request for Continued Examination included herein, Applicant believes no additional fee is due with this response. However, if an additional fee is due, please charge our Deposit Account No. 08-0219, under Order No. 0112981.00125US36 from which the undersigned is authorized to draw.

Respectfully submitted,

Dated: December 21, 2010

/David Giordano/
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